National Drug Monograph
Simeprevir (Olysio™)
November 2014 (Updated)
VA Pharmacy Benefits Management Services,
Medical Advisory Panel, VISN Pharmacist Executives and Office of Public Health

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary[1-2]:

- Simeprevir is a direct acting antiviral; it is a member of the NS3-4A protease inhibitor class similar to boceprevir and telaprevir.
- In November 2013, simeprevir was FDA approved for use in combination with peginterferon alfa and ribavirin for treatment of chronic HCV genotype 1 infection in adult patients with compensated liver disease who are treatment naïve or who have previously failed interferon and ribavirin therapy. Sustained viral response (SVR) was reduced in HCV genotype 1a patients treated with simeprevir with peginterferon alfa and ribavirin who harbored the NS3 Q80K polymorphism at baseline compared to those without the Q80K polymorphism at baseline. It is recommended that baseline screening occurs in HCV genotype 1a patients for the Q80K polymorphism. In patients with the Q80K polymorphism, treatment with simeprevir combined with peginterferon alfa and ribavirin should be avoided. The recommended dose in adults is 150mg mg orally every day with food in combination with peginterferon alfa and ribavirin. The treatment duration of simeprevir with peginterferon alfa and ribavirin is 12 weeks, followed by either 12 or 36 additional weeks of peginterferon alfa and ribavirin, depending on prior response status.
- In the two pivotal Phase 3 clinical trials performed in HCV Genotype 1 patients who were treatment-naïve, the pooled sustained viral response at 12 weeks post-treatment (SVR12) were 80% in the simeprevir with PEG/riba arm and 50% in the PEG/riba group. In the other pivotal Phase 3 clinical trial performed in patients who had relapsed after previous interferon-based HCV treatment, the SVR12 rate in the simeprevir with PEG/riba group was 79% compared to 37% in the PEG/riba group. Based upon these results, simeprevir in combination with PEG/riba was superior to PEG/riba alone in achieving a SVR12 in both HCV treatment naïve subjects and prior relapsers with PEG/riba. Efficacy of simeprevir in combination with PEG/riba was also demonstrated in prior relapsers, partial and null responders to PEG/riba in Phase2b trial.
- In November 2014, simeprevir was FDA approved for use in combination with sofosfovir for treatment of chronic HCV genotype 1 infection in adults with compensated liver diseases who are treatment-naïve or -experienced with or without cirrhosis. Screening patients infected with HCV genotype 1a for the presence of NS3 Q80K polymorphism is not strongly recommended but may be considered. The recommended dose in adults is 150mg orally every day with food in combination with sofosbuvir 400mg orally every day. The treatment duration of simeprevir plus sofosbuvir is 12 weeks in treatment-naïve or –experienced patients without cirrhosis and 24 weeks in treatment-naïve or –experienced patients with cirrhosis.
- The FDA approval of simeprevir in combination with sofosbuvir was based upon a small Phase 2 clinical trial (COSMOS). In patients with Metavir F3, SVR12 was achieved in 94% of patients who received sofosbuvir plus simeprevir with ribavirin for either 12 weeks (15/16) or 24 weeks (16/17). SVR was achieved in 100% of patients who received sofosbuvir plus simeprevir without ribavirin for either 12 weeks (7/7) or 24 weeks (6/6). In patients with Metavir F4 who received sofosbuvir plus simeprevir with ribavirin, SVR12 was achieved in 91% of patients receiving 12 weeks of treatment (10/11) and in 92% of patients receiving 24 weeks (12/13) of treatment. SVR was achieved in 86% (6/7) of patients who received sofosbuvir plus simeprevir without ribavirin for 12 weeks and in 100% (10/10) of those who received this regimen for 24 weeks; however, this represents a difference of only 1 patient.

- Cross-resistance is anticipated amongst available HCV protease inhibitors. Thus, simeprevir should not be used in patients that experienced previous virologic failure with a NS3-4A protease inhibitor containing regimen (e.g., boceprevir or telaprevir).
- Simeprevir has safety considerations with warnings/precautions for potential severe rash and photosensitivity. Other potential adverse events include pruritis, dyspnea and hyperbilirubinemia. Simeprevir has an improved hematologic safety profile compared to boceprevir and telaprevir.
- Due to potential for significant drug-drug interactions, the co-administration of simeprevir must be avoided with moderate or strong inducers or inhibitors of CYP3A.
- Conclusion: In the pivotal phase 3 clinical trials, simeprevir in combination with PEG/riba was superior to PEG/riba alone in achieving SVR in both HCV treatment naïve subjects and prior relapsers with PEG/riba. The FDA indication was extended to prior partial and null responders to PEG/riba based upon Phase2b data. Due to lower SVR rates, HCV genotype 1a patients should receive screening for the Q80K polymorphism at baseline and a treatment with simeprevir combined with peginterferon and ribavirin should be avoided in patients with the Q80K polymorphism. In November 2014, simeprevir in combination with sofosbuvir was FDA approved as an interferon-free regimen based upon results of the Phase 2 clinical trial (COSMOS). In patients receiving simeprevir in combination with sofosbuvir, screening patients infected with HCV genotype 1a for the presence of virus with the NS3 Q80K polymorphism is not strongly recommended but may be considered. Simeprevir containing regimen may cause severe rash and photosensitivity. Patients should limit sun exposure and use sun protective measures during simeprevir therapy.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating simeprevir for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2]

Simeprevir is a direct acting antiviral; it is a member of the NS3-4A protease inhibitor class. Cross-resistance is seen with simeprevir and other available NS3-4A protease inhibitors (i.e., boceprevir and telaprevir).

Table 1. Pharmacokinetics of Simeprevir

Parameter	Simeprevir
Cmin	1936 ng/mL
Tmax	4-6 hours
$AUC_{24hr\ at\ ss}$	57469ng·hr/mL
$T_{1/2}$ (terminal)	41 hours
Protein Binding	>99.8%
Metabolism	Primarily undergoes oxidative metabolism by hepatic CYP3A
Elimination	Feces (91%) and urine (<1%)

FDA Approved Indication[1]

Simeprevir is indicated for the treatment of chronic infection as a component of a combination antiviral regimen.

- Simeprevir efficacy has been established in combination with peginterferon and ribavirin in HCV genotype 1 subjects with compensated liver disease (including cirrhosis); efficacy is influenced by baseline host and viral factors. Simeprevir efficacy has also been established in combination with sofosbuvir in HCV genotype 1 patients. Simeprevir must not be used as monotherapy.
- Simeprevir efficacy, in combination with peginterferon and ribavirin, is substantially reduced in patients infected with HCV genotype 1a with the NS3 Q80K polymorphism at baseline compared to patients without the Q80K polymorphism. Screening patients with HCV genotype 1a infection for the presence of virus with

NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy to simeprevir combined with peginterferon alfa and ribavirin should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.

- Simeprevir should not be used in patients that experienced previous virologic failure with a NS3-4A protease inhibitor containing regimen (e.g., boceprevir or telaprevir).

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM intranet site only).

Potential off-label uses may be in patient populations that were not included in clinical trials including patients co-infected with HIV, hepatitis B or post-liver transplant.

The following guidelines also recommend off-label regimens:

- Chronic Hepatitis C Virus (HCV) Infection: Treatment Considerations from the Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health. Available at http://vaww.hepatitis.va.gov
- IDSA/AASLD Recommendations for Testing, Managing, and Treating Hepatitis C. Available at http://www.hcvguidelines.org

Current VA National Formulary Alternatives

Simeprevir and sofosbuvir; both restricted to CFU.

Dosage and Administration[1-2]

Simeprevir in combination with peginterferon and ribavirin

Simeprevir 150mg orally once daily with food for 12 weeks *plus* peginterferon (either peginterferon alfa-2a 180 mcg/week or alfa-2b 1.5 mcg/kg/week) and ribavirin (in 2 divided doses) with food: <75 kg: 1000 mg/day or ≥75 kg: 1200 mg/day). Treatment duration of simeprevir in combination with peginterferon alfa and ribavirin is 12 weeks, followed by either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on prior response status (Table 2).

Table 2. Duration of Therapy for Simeprevir Regimens containing PEG/riba

Population includes patients with or without cirrhosis	Regimen	Total treatment duration
Treatment-naïve **OR** **Prior Relapser to PEG/riba**[a]	Simeprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 12 weeks	24 weeks
Prior Partial Responder to PEG/riba[b] **OR** **Prior Null Responder to PEG/riba**[c]	Simeprevir plus PEG/riba for 12 weeks, then PEG/riba for an additional 36 weeks	48 weeks
Treatment Futility	**HCV RNA should be monitored at week 4, 12, and 24.** **If HCV RNA ≥ 25 IU/mL at any of these time points, discontinue all treatment**	

[a]Relapser=undetectable HCV-RNA at end of prior treatment with a subsequent detectable HCV-RNA in plasma
[b]Partial responder=decrease in HCV-RNA viral load greater than or equal to 2-log10 by Week 12, but remains detectable thru week 24 or treatment end
[c]Null Responder=decrease of <2 $\log_{10}$ in HCV viral load after 12 weeks of prior HCV therapy with peginterferon and ribavirin
PEG=peginterferon, riba=ribavirin

Simeprevir in combination with sofosbuvir

Table 3. Dosage and Duration of Therapy for Simeprevir plus Sofosbuvir Regimens

Population	FDA approved interferon-free regimens	Total treatment duration
Treatment-naïve and treatment-experienced* patients without cirrhosis	Simeprevir 150mg orally once daily with food *plus* sofosbuvir orally 400mg once daily	12 weeks
Treatment-naïve and treatment-experienced* patients with cirrhosis	Simeprevir 150mg orally once daily with food *plus* sofosbuvir orally 400mg once daily	24 Weeks

*Treatment-experienced patients include prior relapsers, prior partial responders and prior null responders who failed prior IFN-based therapy.

Patients should have HCV RNA assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, HCV RNA should be reassessed in 2 weeks. If the repeated HCV RNA level has increased (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all therapy should be strongly considered.

If any of the other antiviral drugs used in combination with simeprevir for the treatment of chronic HCV infection are permanently discontinued for any reason, simeprevir should also be discontinued.

Hepatic Impairment: No dosage adjustment is necessary for patients with mild hepatic impairment receiving simeprevir. No safety and efficacy available for use of simeprevir in HCV-infected patients with moderate or severe hepatic impairment. HCV-uninfected subjects with moderate or severe hepatic impairment had AUC_{24} of simeprevir 2.4- and 5.2-fold higher, respectively. The prescribing information states that no dose recommendation can be given for patients with moderate severe hepatic impairment (Child-Pugh Class B) due to modest increases in simeprevir exposures; simeprevir is not recommended for patients with severe hepatic impairment (Child-Pugh Class C) due to substantially higher simeprevir exposures. In clinical trials, higher simeprevir exposures have been associated with increased frequency of adverse reactions, including rash and photosensitivity.

Renal Impairment: No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment. Simeprevir has not been evaluated in patients with severe renal impairment (CrCL <30mL/min) or end-stage renal disease, including patients requiring dialysis. Due to simeprevir being highly protein-bound, it is not anticipated to be significantly removed during dialysis.

Prescriptions should be limited to no more a 28-day supply. Store simeprevir capsules in the original bottle in order to protect from light and at room temperature below 30°C (86°F).

Efficacy[1-4]

Simeprevir in combination with peginterferon and ribavirin

The FDA indication was primarily based upon three pivotal phase 3 trials and one phase 2b trials (Table 4). The phase 3 trials were conducted internationally; 20-30% of patients from US in C208/C216 and 18% in HPC3007. Overall, cirrhotic subjects comprised 10-18% of the patients. In the pivotal phase 3 clinical trials, simeprevir in combination with PEG/riba was superior to PEG/riba alone in achieving SVR12 in both HCV treatment naïve subjects and prior relapsers with PEG/riba (Table 5). In treatment-naïve patients, SVR was higher in those with

GT1b versus GT1a (85% vs 75%), IL28b CC versus CT or TT (95% vs 78% and 61%, respectively), and non-cirrhotics (84% vs 60%-65%). In the phase 2b study, partial responders receiving simeprevir plus peginterferon and ribavirin for 12 weeks followed by peginterferon and ribavirin for an additional 36 weeks, had a SVR rate of 65% (15/23); in null responders receiving simeprevir plus peginterferon and ribavirin for 12 weeks followed by peginterferon and ribavirin for an additional 36 weeks, the SVR rate was 53% (9/17).

Table 4: Clinical Trials supporting FDA indications

Clinical Trial	Study	Population	Regimen
Phase 3	C208 (QUEST 1)	Treatment naïve	Simeprevir with PEG/riba compared to PEG/riba alone
Phase 3	C216 (QUEST 2)	Treatment naïve	Simeprevir with PEG/riba compared to PEG/riba alone
Phase 3	HPC 3007 (PROMISE)	Previous relapsers to PEG/riba	Simeprevir with PEG/riba compared to PEG/riba alone
Phase 2b	C206 (ASPIRE)	Previous relapsers, partial and null responders to PEG/riba	Explored various doses and duration of simeprevir with PEG/riba compared to PEG/riba alone

Table 5: Primary efficacy endpoint in Phase 3 clinical trials

Outcome	C208 and C216 N=785		HPC3007 N=393	
	Simeprevir with PEG/riba	PEG/riba	Simeprevir with PEG/riba	PEG/riba
SVR12[a]	419/521 (80%)	133/264 (50%)	206/260 (79%)	49/133 (37%)

[a]Sustained Viral Response (SVR)12 is defined as number of patients with undetectable viral load (i.e, HCV RNA < lower limit of detection) 12 weeks after the actual end of treatment.

Simeprevir in combination with sofosbuvir (COSMOS)[4]

The efficacy and safety of simeprevir is combination with sofosbuvir (with or without ribavirin) in HCV Genotype 1 was evaluated in a small Phase II clinical trial. Patients enrolled were part of the following cohorts 1) prior null responders to PEG/riba with METAVIR score F0-F2 or 2) treatment-naïve patients and prior null responders with METAVIR score F3-F4. Patients were randomized to simeprevir 150mg once daily and sofosbuvir 400mg once daily with or without ribavirin for 12 or 24 weeks.

The demographics of the 80 patients in Cohort 1 (i.e., prior null responders to PEG/riba with METAVIR score F0-F2) were the following: median age 56 years; 61% were male; 71% White, 29% African American, 25% Hispanic; 98% HCV RNA >800,000 IU/mL; 59% METAVIR fibrosis score F2; 78% HCV genotype 1a; 50% genotype 1a with NS3 Q80K polymorphism. All subjects were prior null responders to peg/riba. The demographics of the 87 patients in Cohort 2 (i.e, treatment-naïve patients and prior null responders with METAVIR score F3-F4) were the following: median age 58 years; 67% male; 91% White, 9% African American, 17% were Hispanic; 84% had HCV RNA > 800,000 IU/mL; 47% METAVIR fibrosis score F4; 78% HCV genotype 1a; 40% G1a with NS3 Q80K polymorphism; 54% prior null responders to peg/riba and 46% were treatment-naïve.

The SVR12 in the four treatment arms and two cohorts are listed in Table 6 below. The addition of ribavirin to simeprevir and sofosbuvir did not increase SVRs. Based upon these results, the company pursued phase 3 trials evaluating 8 vs 12 week regimen of SIM/SOF (no ribavirin) in treatment-naïve and -experienced patients with Metavir F0-F3 (Optimist 1) and 12 week regimen of SIM/SOF (no ribavirin) in treatment-naïve and -experienced

patients Metavir F4 (Optimist 2). However, the FDA approved 24 weeks of simeprevir and sofosbuvir for treatment-naïve or –experienced with cirrhosis.

Table 6. Results of SVR at 12 weeks (COSMOS)

	Simeprevir and sofosbuvir *with*out ribavirin for 12 weeks	**Simeprevir and sofosbuvir *with* ribavirin for 12 weeks**	**Simeprevir and sofosbuvir *without* ribavirin for 24 weeks**	**Simeprevir and sofosbuvir *with* ribavirin for 24 weeks**
SVR12				
Prior null responders to PegIFN/RB and METAVIR score F0-F2	13/14 (93%)	26/27 (96%)	14/15(93%)	19/24 (79%)
-G1a subgroup w/Q80K	5/6 (83%)	8/9 (89%)	4/4 (100%)	8/12 (67%)
Treatment-naïve patients and prior null responders with METAVIR score F3-F4	13/14 (93%)	25/27 (93%)	16/16 (100%)	28/30 (93%)
-G1a subgroup w/Q80K	3/3 (100%)	7/8 (88%)	5/5 (100%)	11/11 (100%)

For further details on the simeprevir with PEG/riba efficacy results of the clinical trials, refer to *Appendix*.

Adverse Events (Safety Data)[1-2]

Simeprevir in combination with peginterferon and ribavirin

The safety of simeprevir in combination with PEG/riba has been evaluated in 781 patients during Phase 3 clinical trials. Discontinuations due to adverse events occurred in 2% (14/781) of patients treated with a simeprevir-based regimen compared to 1% (5/397) treated with PEG/riba only. The most common reason for discontinuation in the simeprevir treated group was "rash *excluding* photosensitivity" (n=7).

"Rash *including* photosensitivity" accounted for the most common adverse event reported with simeprevir regimens (refer to Table 7). In comparison, "rash *excluding* photosensitivity" occurred in 25% in the simeprevir-arm compared to 19% in the PEG/riba arm. In the "rash *excluding* photosensitivity" group, four patients experienced Grade 3 adverse events that required discontinuation of therapy while no patients experienced Grade 4 or serious adverse events. During the first 12 weeks of treatment, "photosensitivity" was reported in 38 subjects (5%) in the simeprevir arm compared to 3 subjects (1%) in the PEG/riba group. In the "photosensitivity" adverse event group, one patient had a Grade 3 adverse event while two other patients experienced serious adverse events.

Table 7. Adverse events reported with 3% or higher frequency in simeprevir containing regimens during first 12 weeks (Pooled Phase 3 Trials)

	Simeprevir in combo with peginterferon and ribavirin N=781 **%** (n)	**Placebo in combo with peginterferon and ribavirin** N=397 **%** (n)
Rash (including photosensitivity)	28 (218)	20 (79)
Pruritus	22 (168)	15 (58)
Nausea	22 (173)	18 (70)
Myalgia	16 (126)	13 (53)
Dyspnea	12 (92)	8 (30)

p-values not provided

As shown in Table 8 below, bilirubin elevations occurred at a higher frequency (49%) in patients treated with simeprevir compared to PEG/riba (26%); most bilirubin abnormalities were deemed grade 1 and 2. According to the FDA medical review, elevations in bilirubin typically peaked by Week 2 and return to approximately baseline values four weeks after completion of 12 weeks of simeprevir therapy (i.e., Week 16). Unlike boceprevir and telaprevir, no major differences in hematologic adverse events or hematologic laboratory abnormalities were seen in simeprevir with PEG/riba compared to PEG/riba alone during the first 12 weeks of treatment (Table 9).

Table 8. Laboratory abnormalities reported with 3% or higher frequency in simeprevir containing regimens during first 12 weeks (Pooled Phase 3 Trials)

	Simeprevir in combo with peginterferon and ribavirin N=781 %	**Placebo in combo with peginterferon and ribavirin N=397 %**
Alkaline phosphatase		
Grade 1 (>1.25 to ≤2.50 x ULN)	3	1
Grade 2 (>2.50 to ≤5.00 x ULN)	<1	0
Hyperbilirubinemia		
Grade 1 (>1.1 to ≤1.5 x ULN)	27	15
Grade 2 (>1.5 to ≤2.5 x ULN)	18	9
Grade 3 (>2.5 to ≤5.0 x ULN)	4	2
Grade 4 (≥ 5.0 x ULN)	<1	0

ULN: upper limit of normal; p-values not provided

Table 9: Hematologic Laboratory Abnormalities during First 12 weeks of therapy

	Simeprevir in combo with peginterferon and ribavirin N=781 %	**Placebo in combo with peginterferon and ribavirin N=397 %**
Hemoglobin		
Grade 1 (9.5-10.5 gm/dL)	121 (15%)	59 (15%)
Grade 2 (8 to <9.5 gm/dL)	41 (5%)	19 (5%)
Grade 3 (6.5 to < 8 gm/dL)	6 (1%)	7 (2%)
Neutrophils (x10^9/L)		
Grade 1 (1000-1500/mm^3)	314 (40%)	149 (38%)
Grade 2 (750-999/mm^3)	159 (20%)	93 (23%)
Grade 3 (500-749/mm^3)	96 (12%)	52 (13%)
Grade 4 (<500/mm^3)	23 (3%)	11 (3%)
Platelets (x10^9/L)		
Grade 1 (75,000 to <100,000)	101 (13%)	54 (14%)
Grade 2 (50,000 to < 75,000)	44 (6%)	37 (9%)
Grade 3 (20,000 to <50,000)	13 (2%)	3 (1%)

p-values not provided

Deaths and Other Serious Adverse Events (SAEs)[1-2]

In phase 3 clinical trials, three deaths in occurred in simeprevir arm and none in placebo arm. None of the deaths were considered related to simeprevir. Serious adverse events occurred in 2% (16/781) of patients receiving

simeprevir-containing regimen and 3% (10/397) in patients receiving PEG/riba. The investigators indicated that only three SAE were considered related to simeprevir therapy. Two patients experienced photosensitivity related SAEs during first 12 weeks of simeprevir therapy; both patients required hospitalization and one patient received systemic steroids. Another patient experienced major depression.

Simeprevir in combination with sofosbuvir (COSMOS)

The most common (>10%) adverse reactions reported with simeprevir plus sofosbuvir without ribavirin for 12 weeks were fatigue (25%), headache (21%), nausea (21%), insomnia (14%), pruritus (11%) and rash (11%). Photosensitivity was reported in 7% of subjects. In addition, dizziness (16%), and diarrhea (16%) were commonly reported in patients receiving simeprevir plus sofosbuvir for 24 weeks.

Contraindications[1]

- Simeprevir should always be administered in combination with other antiviral drugs for the treatment of chronic HCV infection; prescribers should consult the complete prescribing information for these drugs for a description of contraindications.
- All contraindications to peginterferon and ribavirin also apply when simeprevir is administered with peginterferon and ribavirin**.** Because ribavirin may cause birth defects and fetal death, simeprevir in combination with peginterferon alfa and ribavirin is contraindicated in pregnant women and in men whose female partners are pregnant.

Warnings and Precautions[1]

- **Risk of Serious Adverse Reactions Associated With Combination Treatment:** Simeprevir should be used in combination with other antiviral drugs for the treatment of chronic HCV infection. Therefore, consult the prescribing information for these drugs before starting therapy with simeprevir. Warnings and Precautions related to these drugs also apply to their use in simeprevir combination treatment.
- **Pregnancy:** Ribavirin may cause birth defects and/or death of the exposed fetus; avoid pregnancy in female patients and in female partners of male patients. Ribavirin therapy should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Women of childbearing potential and men must use at least two forms of effective contraception during treatment and for at least 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time.
- **Photosensitivity:** Photosensitivity including severe reactions that required hospitalization have been observed with simeprevir containing therapy. Photosensitivity reactions occurred most frequently in the first 4 weeks of treatment with simeprevir containing therapy but can occur at any time during treatment. It may present as an exaggerated sunburn reaction typically occurring in areas exposed to the sun such as the face, neck, forearms, and hands. Manifestations may include burning, erythema, exudation, blistering, and edema. Use sun protective measures and limit sun exposure during treatment with simeprevir therapy. Avoid use of tanning devices. Discontinuation of simeprevir should be considered if a photosensitivity reaction occurs and patients should be monitored until the reaction has resolved. If a decision is made to continue simeprevir in the setting of a photosensitivity reaction, expert consultation is advised.
- **Rash:** Rash including severe rash that required discontinuation has been observed with simeprevir containing therapy. Similar to photosensitivity, rash occurred most frequently in the first 4 weeks of treatment with simeprevir, but can occur at any time during treatment. Patients with mild to moderate rashes should be followed for possible progression of rash, including the development of mucosal signs (e.g., oral lesions, conjunctivitis) or systemic symptoms. If the rash becomes severe, simeprevir should be discontinued. Patients should be monitored until the rash has resolved.
- **Sulfa Allergy:** Simeprevir contains a sulfonamide moiety. In subjects with a history of sulfa allergy (n=16), no increased incidence of rash or photosensitivity reactions has been observed. However, there are

insufficient data to exclude an association between sulfa allergy and the frequency or severity of adverse reactions observed with the use of simeprevir.

- **Use with peginterferon alfa and ribavirin:** Simeprevir must NOT be used as monotherapy. According to prescribing information, it should be used in combination with peginterferon and ribavirin. Refer to prescribing information of peginterferon and ribavirin before starting therapy.
- **Drug interactions:** Avoid co-administration of simeprevir with moderate or strong inducers or inhibitors of CYP3A.

Special Populations[1]

- **Pregnancy Category**
  - Pregnancy category X when simeprevir used with ribavirin and peginterferon (as ribavirin is pregnancy category X). Simeprevir in combination with ribavirin and peginterferon should not be started unless a report of a negative pregnancy test has been obtained immediately prior to initiation of therapy. Two effective methods of contraception should be used during treatment with simeprevir and concomitant ribavirin, and for 6 months after treatment has concluded. Routine monthly pregnancy tests must be performed during this time.
  - Pregnancy category C for simeprevir
- **Nursing mothers:** It is unknown whether simeprevir is excreted in human breast milk. Due to potential for adverse reactions in nursing infants, decision of discontinuing nursing or therapy with simeprevir should be made.
- **Race:** HCV-infected patients of East Asian ancestry had AUC_{24} of simeprevir 3.4-folder higher. Insufficient data to recommend reduce dose in this population; risk and benefits should be considered prior to use.
- **Hepatic Impairment:** Refer to Dosage and Administration section.
- **Renal Impairment:** No dosage adjustment is necessary for patients with mild, moderate or severe renal impairment; simeprevir was not studied in patients with severe renal impairment (<30mL/min), end-stage renal disease or on hemodialysis. Due to simeprevir being highly protein-bound, it is not anticipated to be significantly removed during dialysis.
- **Geriatrics:** Limited data in patients ≥ 65 years old; no dose adjustment is necessary in this age group.
- **Gender, Body Weight, or Body Mass Index:** No dosage adjustment is necessary.
- **Liver Transplantation:** No efficacy and safety data available in this patient population.
- **Other HCV genotypes:** No efficacy and safety data with other HCV genotypes.

Postmarketing Safety Experience

No data.

Sentinel Events

No data.

Look-alike / Sound-alike (LA / SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Simeprevir 150mg cap	Non	None	None	Telaprevir, Saquinavir, Sevelamir, Sofosbuvir
Olysio	None	None	None	Onglyza

Drug-Drug Interactions[1-2]

Simeprevir is a substrate and mild inhibitor of CYP3A and substrate and inhibitor of P-gp and OATP1B1/3. Co-administration of simeprevir with agents that are moderate or strong inducers or inhibitors of CYP3A is not recommended. Refer to prescribing information for more detailed and comprehensive information.

- A brief summary of drugs that should not be co-administered with simeprevir include certain anticonvulsants (carbamazepine, oxcarbazepine, phenobarbital, phenytoin), systemic azole antifungals (itraconazole, ketoconazole, posaconazole, fluconazole, voriconazole), certain macrolides (erythromycin, clarithromycin, telithromycin), rifamycins (rifampin, rifabutin, rifapentine), systemic dexamethasone, cisapride, milk thistle, and St. John's wort. HIV medications that should not be co-administered include elvitegravir/cobicistat/emtricitabine/tenofovir, non-nucleoside reverse transcriptase inhibitors (efavirenz, delavirdine, etravirine, nevirapine) and any HIV protease inhibitors with or without ritonavir.
- Other medications that require caution and close monitoring including therapeutic drug monitoring (if applicable) include digoxin, antiarrhythmics (amiodarone, disopyramide, flecainide, mexiletine, propafenone, quinidine), warfarin, calcium channel blockers (amlodipine, diltiazem, felodipine, nicardipine, nifedipine, nisoldipine, verapamil, oral administration of triazolam and midazolam, cyclosporine, tacrolimus, sirolumus.
- PDE-5 inhibitors may be needed dose adjustment when used for treatment of pulmonary arterial hypertension.
- Concentrations of HMG CO-A reductase inhibitors increase with co-administration of simeprevir. Titrate statin dose carefully and monitor for safety. Use lowest dose possible. Do not exceed the following daily doses: 10mg for rosuvastatin and 40mg for atorvastatin.

Pharmacoeconomic Analysis

The VHA Office of Public Health has the following resource for VA facilities: National Hepatitis C Registry Reports are generated from the national Clinical Case Registry (CCR) for Hepatitis C by the Population Health of the Office of Public Health. The current reports describe basic demographics, mortality, treatment, conditions commonly seen in patients with hepatitis C and selected measures of clinic care. These reports are intended to provide information that will be of interest and use to providers and administrators of care as they plan and deliver services to Veterans with hepatitis C. The 2014 report data are posted on intranet site at the following link. http://vaww.hepatitis.va.gov/data-reports/ccr-index.asp Choose the report and then scroll down to VISN/Facility specific data.

Acquisition Costs

Refer to VA pricing sources for updated information.

Conclusions[1-4]

Conclusion: In the pivotal phase 3 clinical trials, simeprevir in combination with PEG/riba was superior to PEG/riba alone in achieving SVR in both HCV treatment naïve subjects and prior relapsers with PEG/riba. The FDA indication was extended to prior partial and null responders to PEG/riba based upon Phase2b data. Due to lower SVR rates, HCV genotype 1a patients should receive screening for the Q80K polymorphism at baseline and a treatment with simeprevir combined with peginterferon and ribavirin should be avoided in patients with the Q80K polymorphism. In November 2014, simeprevir in combination with sofosbuvir was FDA approved as an interferon-free regimen based upon results of the Phase 2 clinical trial (COSMOS). In patients receiving simeprevir in combination with sofosbuvir, screening patients infected with HCV genotype 1a for the presence of virus with the NS3 Q80K polymorphism is not strongly recommended but may be considered. Simeprevir containing regimen may cause severe rash and photosensitivity. Patients should limit sun exposure and use sun protective measures during simeprevir therapy.

References:

1. Olysio (Simeprevir) package insert, Janssen Therapeutics Inc. November 2014.

2. FDA product review documents. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/205123Orig1s000TOC.cfm
3. Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 Infection: a phase IIb Trial. Gastroenterology 2014;146:430-441.
4. Lawitz E, Sulkowski MS, Ghalib R et al. Simeprevir plus sofosbuvir, with or without ribavirin, to treat chronic infection with hepatitis C virus genotype 1 in non-responders to pegylated interferon and ribavirin and treatment-naive patients: the COSMOS randomised study. Lancet 2014;384:1756-65.

Prepared February 2014; Contact Melinda Neuhauser, PharmD, MPH

Appendix. Clinical Trials

Citation	**Phase 3 Clinical Trial: C208 and C216** (Pooled efficacy analysis; both performed in a HCV treatment-naïve population and nearly identical study design per FDA medical review) Please note that the results of these phase III trial have not been published, and data were obtained from FDA drug application and product insert
Study Goals	Demonstrate the superiority of simeprevir versus placebo as part of a treatment regimen including PEG/riba
Study Design	Multicenter, phase 3, randomized, double-blind controlled trial comparing simeprevir in combination with PEG/rib compared to placebo in combination with PEG/riba in HCV Genotype 1 patients who are *treatment-naïve* with compensated liver disease including cirrhosis
Methods	**Treatment:** Simeprevir arm: Patients received 12 weeks of simeprevir in combination with PEG/riba followed by an additional 12 or 36 weeks of PEG/riba based upon a predefined response guided algorithm. HCV therapy was stopped at Week 24 in the simeprevir group in accordance with the response guided algorithm if HCV RNA levels < 25 IU/mL were achieved at Week 4 AND were undetectable at Week 12; patients not meeting these criteria were continued PEG/riba for a total of 48 weeks of therapy. Stopping (futility) rules included an HCV RNA >1000 IU/mL at week 4, an HCV RNA <2 log10 IU/mL at week 12, or HCV RNA ≥25 IU/mL at week 24 or 36. Placebo arm: Patients received 12 weeks of placebo in combination with PEG/riba followed by 36 weeks of PEG/riba. **Primary efficacy endpoint:** - Sustained virologic response 12 weeks after the planned end of treatment (SVR12) in the intent-to-treat population. **Secondary efficacy endpoints** - Proportion of patients with on-treatment failure - Proportion of patients with viral relapse - Sustained virologic response 24 weeks after the planned end of treatment (SVR24) - Sustained virologic response 72 weeks after the planned end of treatment (SVR72) **Randomization** - 2:1 allocation ratio (simeprevir: placebo) with stratification factors for HCV genotype/subtype (1a, 1b, other) and IL28B (CC, CT, TT). - For C216 trial, patients in European countries were also randomized in 1:1 ratio to peginterferon alpha-2a or peginterferon alpha-2b **Statistical analysis:** - The study was designed to detect a difference of at least 20% in SVR12 between treatment arms at the 2-sided 5% significance level with >90% power.
Criteria	**Inclusion criteria** - Not available **Exclusion criteria** - Liver disease of non-HCV etiology - HBV co-infection - HIV co-infection
Results	**Demographics**

	C208 and C216 N=785	
	Simeprevir with PEG/riba	PEG/riba
Gender n (%)		
Male	288 (55%)	151 (57%)
Race n (%)		
Caucasian	464 (89%)	245 (93%)
Black	43 (8%)	14 (5%)
Asian	7 (1%)	4 (2%)
Other	5 (<1%)	1 (<1)
Age (years)		
Median (min, max)	48 (18, 73)	47 (19, 73)
Baseline BMI		
<25 kg/m^2	207 (40%)	103 (39%)
≥25 - <30kg/m^2	201 (39%)	89 (34%)
≥30kg/m^2	113 (22%)	70 (27%)
Geographical Region n (%)		
North America	168 (32%)	86 (33%)
Europe	276 (53%)	142 (54%)
South America	41 (8%)	19 (7%)
Asia-Pacific	36 (7%)	17 (6%)
IL-28B Genotype		
CC	152 (29%)	79 (30%)
CT	292 (56%)	147 (56%)
TT	77 (15%)	38 (14%)
HCV Genotype Subtype		
1a	252 (48%)	128 (48%)
1b	267 (51%)	133 (50%)
Metavir Fibrosis Score		
F0-F1	248 (48%)	110 (42%)
F2	130 (25%)	82 (31%)
F3	82 (16%)	40 (15%)
F4	48 (9%)	32 (12%)
Baseline HCV RNA		
<400,000	59 (11%)	38 (14%)
≥400,000 - ≤800,000	45 (9%)	32 (12%)
>800,000	417 (80%)	194 (73%)

Results of Primary and Select Secondary Efficacy Endpoints

Outcome	C208 and C216 N=785	
	Simeprevir with PEG/riba	PEG/Riba

	Primary Efficacy Endpoint
	SVR12[a] — 419/521 (80%)[b] — 133/264 (50%)
	Secondary Efficacy Endpoints
	On-treatment failure[c] — 43/521 (8%) — 88/264 (33%)
	Viral Relapse — 55/469 (12%) — 38/171 (22%)
	SVR24[d] — 411/500 (82%) — 46/91 (51%)

[a]Sustained Viral Response (SVR)12 is defined as number of patients with undetectable viral load (i.e, HCV RNA < 25 IU/mL) 12 weeks after the actual end of treatment.
[b]SVR12 results were pooled for patients who received simeprevir with 24 or 48 weeks of PEG/riba per the response guided therapy (RGT) rules; 85 - 91% of patients met criteria for RGT and the SVRs in patients meeting RGT criteria were 86 - 91%.
[c]On-treatment failure is defined as number of patients with detectable HCV RNA at end of therapy
[d]Per FDA medical review, in complete data available due to on-going clinical trial

Simeprevir containing regimen was statistically significant in achieving SVR over PEG/riba alone in various subpopulations (i.e., sex, age, race HCV genotype/subtype, IL28B genotype, baseline HCV RNA or Metavir score). An exception was patients who harbored the Q80K polymorphism had no statistically significant difference in SVR12 rates with simeprevir containing regimens compared to PEG/riba.

Results of SVR12 based upon Genotype/subtype and presence of Q80K

Outcome	**C208 and C216 N=785**	
	Simeprevir with PEG/riba	PEG/riba
Genotype 1	419/521 (80%)	133/264 (50%)
Genotype 1a	191/254 (75%)	63/131 (48%)
-W/out Q80K	138/165 (84%)	36/83 (43%)
-With Q80K	49/84 (58%)	24/44 (55%)
Genotype 1b	228/267 (85%)	70/133 (53%)

Conclusion	In the pivotal phase 3 clinical trials, simeprevir in combination with PEG/riba was superior to PEG/riba alone in achieving SVR in HCV treatment-naïve subjects. However, no statistically significant difference was seen in simeprevir-treated patients harboring the Q80K polymorphism compared to the PEG/riba-treated group.

Citation	**Phase 3 Clinical Trial: HPC3007** Please note that the results of the phase III trial have not been published, and data were obtained from FDA drug application and product insert
Study Goals	Demonstrate the superiority of simeprevir versus placebo as part of a treatment regimen including PEG/riba
Study Design	Multicenter, phase 3, randomized, double-blind controlled trial comparing simeprevir in combination with PEG/rib compared to placebo in combination with PEG/riba in HCV Genotype 1 patients *who relapsed following previous interferon-based therapy* with compensated liver disease including cirrhosis
Methods	Refer to C208 methods in above table; Per FDA medical review, the study design of HPC3007 clinical trial was almost identical to that of C208 with the exception that patient population included only patients who received at least 24 weeks of a peginterferon-based therapy and

<table>
<tr><td></td><td>relapsed within 1 year.</td></tr>
<tr><td>Criteria</td><td>Refer to C208 inclusion and exclusion criteria above</td></tr>
<tr><td>Results</td><td>Demographics
<table>
<tr><td></td><td colspan="2">HPC3007
N=393</td></tr>
<tr><td></td><td>Simeprevir with PEG/riba
N=260</td><td>PEG/riba
N=133</td></tr>
<tr><td colspan="3">Gender n (%)</td></tr>
<tr><td>Male</td><td>179 (69%)</td><td>79 (59%)</td></tr>
<tr><td colspan="3">Race n (%)</td></tr>
<tr><td>Caucasian</td><td>243 (93%)</td><td>128 (96%)</td></tr>
<tr><td>Black</td><td>7 (3%)</td><td>4 (3%)</td></tr>
<tr><td>Asian</td><td>8 (3%)</td><td>1 (1%)</td></tr>
<tr><td>Other</td><td>2 (1%)</td><td>0 (0%)</td></tr>
<tr><td colspan="3">Age (years)</td></tr>
<tr><td>Median (min, max)</td><td>52 (20, 70)</td><td>52 (21,71)</td></tr>
<tr><td colspan="3">Baseline BMI</td></tr>
<tr><td><25 kg/m^2</td><td>78 (30%)</td><td>45 (34%)</td></tr>
<tr><td>≥25 - <30kg/m^2</td><td>116 (45%)</td><td>52 (39%)</td></tr>
<tr><td>≥30kg/m^2</td><td>66 (25%)</td><td>36 (27%)</td></tr>
<tr><td colspan="3">Geographical Region n (%)</td></tr>
<tr><td>North America</td><td>53 (20%)</td><td>33 (25%)</td></tr>
<tr><td>Europe</td><td>184 (71%)</td><td>90 (68%)</td></tr>
<tr><td>South America</td><td>0 (0%)</td><td>0 (%)</td></tr>
<tr><td>Asia-Pacific</td><td>23 (9%)</td><td>10 (8%)</td></tr>
<tr><td colspan="3">IL-28B Genotype</td></tr>
<tr><td>CC</td><td>62 (24%)</td><td>34 (26%)</td></tr>
<tr><td>CT</td><td>167 (64%)</td><td>83 (62%)</td></tr>
<tr><td>TT</td><td>31 (12%)</td><td>16 (12%)</td></tr>
<tr><td colspan="3">HCV Genotype Subtype</td></tr>
<tr><td>1a</td><td>110 (42%)</td><td>54 (41%)</td></tr>
<tr><td>1b</td><td>149 (57%)</td><td>79 (59%)</td></tr>
<tr><td colspan="3">Metavir Fibrosis Score</td></tr>
<tr><td>F0-F1</td><td>87 (33%)</td><td>47 (35%)</td></tr>
<tr><td>F2</td><td>80 (31%)</td><td>51 (38%)</td></tr>
<tr><td>F3</td><td>44 (17%)</td><td>15 (11%)</td></tr>
<tr><td>F4</td><td>39 (15%)</td><td>19 (14%)</td></tr>
<tr><td colspan="3">Baseline HCV RNA</td></tr>
<tr><td><400,000</td><td>21 (8%)</td><td>9 (7%)</td></tr>
<tr><td>≥400,000 - ≤800,000</td><td>20 (8%)</td><td>14 (11%)</td></tr>
<tr><td>>800,000</td><td>219 (84%)</td><td>110 (83%)</td></tr>
</table>
Results of Primary and Select Secondary Efficacy Endpoints</td></tr>
</table>

Outcome	HPC3007 N=393	
	Simeprevir with PEG/riba	PEG/riba
Primary Efficacy Endpoint		
SVR12[a]	206/260 (79%)[b]	49/133 (37%)
Secondary Efficacy Endpoints		
On-treatment failure[c]	8/260 (3%)	38/133 (29%)
Viral Relapse	48/249 (19%)	43/90 (48%)
SVR24[d]	199/254 (78%)	20/64 (31%)

[a]Sustained Viral Response (SVR)12 is defined as number of patients with undetectable viral load (i.e, HCV RNA < 25 IU/mL) 12 weeks after the actual end of treatment.
[b]SVR12 results were pooled for patients who received simeprevir with either 24 or 48 weeks of PEG/riba per the response guided therapy (RGT) rules; 93% of patients met RGT criteria for and SVRs in these patients were 83%.
[b]On-treatment failure is defined as number of patients with detectable HCV RNA at end of therapy
[c]Per FDA medical review, in complete data available due to on-going clinical trial

Simeprevir containing regimen was statistically significant in achieving SVR over PEG/riba alone in various subpopulations (i.e., sex, age, race HCV genotype/subtype, IL28B genotype, baseline HCV RNA or Metavir score). One exception is that patients who harbored the Q80K polymorphism had no statistically significant difference in SVR12 rates with simeprevir containing regimens compared to PEG/riba.

Results of SVR12 based upon Genotype/subtype and presence of Q80K

Outcome	HPC3007 N=393	
	Simeprevir with PEG/riba	PEG/riba
Genotype 1	206/260 (79%)	48/133 (36%)
Genotype 1a	78/111 (70%)	14/54 (26%)
-W/out Q80K	62/79 (78%)	8/34 (24%)
-With Q80K	14/30 (47%)	6/20 (30%)
Genotype 1b	128/149 (86%)	34/79 (43%)

Conclusion	In the pivotal phase 3 clinical trials, simeprevir in combination with PEG/riba was superior to PEG/riba alone in achieving SVR in HCV patients who relapsed following previous interferon-based therapy. However, no statistically significant difference was seen in simeprevir-treated patients harboring the Q80K polymorphism compared to the PEG/riba-treated group.

Citation	**Phase 2b Clinical Trial: C206** Zeuzem S, Berg T, Gane E, et al. Simeprevir increases rate of sustained virologic response among treatment-experienced patients with HCV genotype-1 Infection: a phase 2b Trial. Gastroenterology 2014;146:430-441.
Study Goals	Evaluate the efficacy and safety of simeprevir compared to placebo as part of a treatment

<table>
<tr><td></td><td>regimen including PEG/riba</td></tr>
<tr><td>Study Design</td><td>Multicenter, phase 2b, randomized, double-blind controlled trial comparing different regimens of simeprevir in combination with PEG/rib compared to placebo in combination with PEG/riba in HCV Genotype 1 patients who failed to respond or relapsed following previous interferon-based therapy</td></tr>
<tr><td>Methods</td><td>Treatment: Patients were randomized to 6 simeprevir regimens and 1 placebo group.

Simeprevir arms: Patients were randomized to simeprevir 100mg or 150mg daily for 12, 24, or 48 weeks in combination with PEG/riba.

Placebo arm: Patients received 12 weeks of placebo in combination with PEG/riba followed by 36 weeks of PEG/riba.

Futility Rules for discontinuing regimen
<table>
<tr><td>Futility Rule</td><td></td></tr>
<tr><td>Week 4</td><td><1 $\log_{10}$ IU/mL reduction in HCV RNA compared to baseline</td></tr>
<tr><td>Week 12</td><td><2 $\log_{10}$ IU/mL reduction in HCV RNA compared to baseline</td></tr>
<tr><td>Week 24</td><td>Confirmed detectable HCV RNA (≥10 IU/mL)</td></tr>
<tr><td>Week 36</td><td>Confirmed detectable HCV RNA (≥10 IU/mL)</td></tr>
<tr><td>Viral breakthrough (Day 1 to Week 48)</td><td>Confirmed increase in HCV RNA >1 $\log_{10}$ IU/mL compared with lowest on-treatment value OR
Confirmed HCV RNA level of >100 IU/mL if previously lower limit of quantification (25 IU/mL) or undetectable (<10 IU/mL)</td></tr>
</table>
Primary efficacy endpoint:
- Sustained virologic response 24 weeks after the planned end of treatment (SVR24) in the intent-to-treat population.

Secondary efficacy endpoints
- Proportion of patients with rapid viral response (HCV RNA undetectable at week 4)
- Proportion of patients with viral relapse and breakthrough
- Sustained virologic response 12 weeks after the planned end of treatment (SVR12)

Randomization
- 1:1 allocation ratio for various regimens with stratification factors for HCV genotype/subtype (1a, 1b, other) and prior PEG/riba treatment response (i.e., partial response, prior relapse, or null response)

Statistical analysis:
The study was designed to detect a difference of at the 0.83% significance level (5% overall significance adjusted for six multiple comparisons).</td></tr>
<tr><td>Criteria</td><td>Inclusion:
- Adults aged 18- 70 years old
- Chronic HCV Genotype 1
- HCV RNA >10,000 IU/mL
- Received at least one prior course of PEG/riba for ≥12 consecutive weeks and not discontinued to tolerability
Exclusion:
- Decompensated liver disease</td></tr>
</table>

- Liver disease of non-HCV etiology
- Co-infected with hepatitis B and/or HIV
- History of invasive malignancy within 5 years
- Hepatocellular carcinoma
- Pre-existing medical conditions including psychiatric disorders, cardiac, pulmonary, renal impairment
- Laboratory abnormalities
- Organ transplant recipients

Results

Demographics

	All patients N=462
Gender n (%)	
Male	311 (67.3%)
White	428 (92.6%)
Age (years)	
Median (min, max)	50 (20-69)
Baseline BMI	
Median (min, max)	27.2 (18.2-48.7)
Prior response to PEG/riba	
Null response	117 (25.3%)
Partial response	160 (34.6%)
Relapse	185 (40.0%)
IL-28B Genotype (n=328 patients)	
CC	58 (17.7%)
CT	212 (64.6%)
TT	58 (17.7%)
HCV Genotype Subtype (n=455 patients)	
1a	188 (41.3%)
1b	262 (57.6%)
Metavir Fibrosis Score (n=455 patients)	
F3	86 (18.9%)
F4	83 (18.2%)
Baseline HCV RNA	
>800,000	399 (86.4%)

Results of Primary Efficacy Endpoint

Outcome	**HPC3007 N=393**	
	Simeprevir with Peg/riba (includes all regimens)	Peg/riba
Primary Efficacy Endpoint; SVR 24		
Overall	61-80%	23%[a]
Prior null response	38-59%	19%
Prior partial response	48-86%	9%
Prior relapse	77-89%	37%

[a]p-value: <0.001

<table>
<tr><td></td><td>Limited data was available in this trial for patients having baseline Q80K polymorphism. Unlike the Phase 3 clinical trials, patients receiving simeprevir 150mg with PEG/riba with and without Q80K had similar SVRs.

<u>Results of SVR24 based upon Genotype/subtype and presence of Q80K</u>
<table>
<tr><td></td><td>Simeprevir 150mg with PEG/riba</td></tr>
<tr><td colspan="2">Genotype 1a</td></tr>
<tr><td>-W/out Q80K</td><td>39/59 (66.1%)</td></tr>
<tr><td>-With Q80K</td><td>14/23 (60.9%)</td></tr>
</table></td></tr>
<tr><td>Conclusion</td><td>Overall, simeprevir containing regimens achieved higher SVR24 than PEG/riba therapy in treatment-experienced patients.</td></tr>
</table>